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Reconsideration of interferon treatment for viral diseases: Lessons from SARS, MERS, and COVID-19

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ABSTRACT

Periodic pandemics of coronavirus (CoV)–related pneumonia have been a major challenging issue since the outbreak of severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012. The ongoing pandemic of CoV disease (COVID-19) poses a substantial threat to public health. As for the treatment options, only limited antiviral agents have been approved hitherto, and clinicians mainly focus on currently available drugs including the conventional antiviral interferons (IFNs). In clinical practice, IFNs, when used either alone or in combination with ribavirin and/or lopinavir/ritonavir, have shown promising outcomes, to some extent, in SARS-CoV or MERS-CoV treatment. Although the efficacy and safety of IFNs in COVID-19 treatment remain unclear, their possible use merits further evaluation. We present a review that summarizes current evidence of IFN treatment for COVID-19 and elaborates on other challenges in terms of the timing of IFN treatment initiation, treatment duration, and IFN type to be used. The review findings suggested that IFN acts by directly inhibiting viral replication and activating immune cell subsets. However, there is a lack of well-designed and controlled clinical trials providing firm evidence for the efficacy or safety of IFN therapy for CoVs. Additionally, critically ill patients with multiple immunosuppression-associated comorbidities may not benefit from IFN therapy, necessitating screening of those patients who would most benefit from IFN treatment.

1. Introduction

The ongoing pandemic of coronavirus (CoV) disease (COVID-19), which started in December 2019, was caused by an outbreak of infection due to novel CoV, which was later officially named by the World Health Organization (WHO) as severe acute respiratory syndrome CoV-2 (SARS-CoV-2) [1]. Early reports of the highly pathogenic COVID-19 included the SARS epidemic in late 2002 and Middle East respiratory syndrome (MERS) in 2012 [2,3]. Owing to their unprecedented speed and range of transmission,CoV infections are associated with a high fatality rate and are widely distributed across geographic regions, both of which pose a major threat to healthcare systems and economies.

One of the major challenging issues in the management of COVID-19 is that effective therapeutic regimens are not yet fully established. Even though new drugs such as Paxlovid^{TM} (nirmatrelvir/ritonavir) are approved for emergency use, data on their actual effect are insufficient and controversial [4]. Most of the currently available treatment options for COVID-19, such as interferons (IFNs) and other antiviral agents, are extrapolated from evidence accumulated during the SARS and MERS epidemics [5]. Physiologically, IFNs are important components of our innate and adaptive immune systems, and exogenously administered IFNs are effective in reducing viral replication and disease severity [6]. Therefore, IFNs are one of the most widely used therapeutic regimens for COVID-19.

This review provides an overview of the theoretical basis of IFN therapy for COVID-19 as well as evidence from in vitro, animal, and clinical studies (Fig. 1). By compiling accumulated information, our review also elaborates on the factors that could significantly affect therapeutic outcomes, such as the route and approach of IFN administration, the timing of IFN initiation, and the duration of IFN treatment, and so on. Given the scenario of the ongoing aggressive COVID-19 pandemic, the findings of this review may help pave the way for more opportunities and consideration of IFN treatment for CoV infections, especially in future clinical trials.

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2. COVID-19

CoVs are a group of enveloped, positive-sense single-stranded RNA viruses that are named after their corona-like morphological appearance [7]. They are zoonotic pathogens and can be transmitted from animals to humans, wherein they cause a spectrum of illnesses ranging from being asymptomatic to severe and often fatal respiratory and enteric diseases in their new hosts. In the past decades, pneumonia caused by the highly pathogenic CoV emerged periodically in different areas worldwide and posed substantial challenges to public health. Since the emergence of SARS, the WHO has recorded 8000 or more cases of SARS-CoV infection and approximately 800 associated deaths [8,9]. As of August 2022, the WHO has recorded 2591 laboratory-confirmed MERS cases in 27 countries, with 894 associated deaths [10]. The cumulative number of COVID-19 cases in 196 countries and regions as of October 07, 2022, was 620,471,620, and the total number of associated deaths was 6,554,523 [11].

A patient with COVID-19 may remain asymptomatic in the early stage of the disease until symptoms such as severe pneumonia, dyspnea, septic shock, multiorgan insufficiency and even death occur [12,13]. Initially, most of the infected patients experience flu-like symptoms, commonly including fever, chills, headaches and cough. Some of the cases then rapidly progress into severe pneumonia and acute respiratory distress, and many people with such conditions may require mechanical ventilation [14]. The mortality rate is higher among elderly and comorbid patients, which may be attributed to their compromised immune system and the inhibition of type I IFN signaling by their antibodies, resulting in a significantly increased viral load [15–18]. Hence, COVID-19 is a severe health problem that requires great attention from the public and clinical investigators.

3. Theoretical basis of IFN treatment for COVID-19

IFNs are classified into type I IFNs (-α, -β, -δ, -ε, -ζ, -κ, -τ, and -ω), type II IFN (-γ), and type III IFNs (-λ1, -λ2, -λ3, and -λ4) according to the type of receptors through which they initiate signaling [19]. Traditionally, IFNs, especially type I IFNs, have been widely used to treat viral hepatitis, malignancies such as leukemia and renal cell carcinoma, and multiple sclerosis [20]. Their efficacy against CoVs is being tested in an ongoing clinical trial, based on their general ability to inhibit viral replication and activate immune cell populations to eliminate viral infections.

IFNs predominantly participate in the host defense function against viral invasion. CoVs first fuse with the cellular membrane and then interact with innate pattern recognition receptors to enter the cells. After viral invasion, considerable levels of type I IFNs and moderate levels of type III IFNs are rapidly produced by stromal cells or professional antigen-presenting cells, triggering strong antiviral innate immune responses [12,21–23]. IFNs can upregulate the expression of more than 300 IFN-stimulated genes (ISGs), leading to the secretion of potent antiviral proteins [24], thus providing first-line defense against diverse pathogens (Fig. 2). Molecules of the type I IFN pathway play critical roles in protecting developing fetuses and resisting SARS-CoV-2 infection in the placenta [25]. Indeed, dysregulation of the IFN response can increase viral virulence [19]. In MERS-CoV–infected mice, blockade of IFN-I signaling delayed clearance of the virus, increased neutrophil infiltration, and impaired MERS-CoV–specific T-cell responses [26]. In patients with moderate COVID-19, physiological levels of IFN-α exerted immunoregulatory effects by suppressing SARS-CoV-2 replication in human airway cells [27]. Reportedly, in patients with COVID-19, SARS-CoV-2 can block the production of IFNs and reduce effective adaptive immune responses by activating the innate immune system through the renin-angiotensin and kinin-kallikrein pathways [28]. Consistently, one patient who had a surging production of IFN-α had a successful clearance of MERS-CoV, whereas another patient who had a decreased production of IFN-α died, which confirms the therapeutic role of IFNs [29]. Type I IFNs not only act as direct antiviral messengers but also promote phagocytosis of macrophages and apoptosis of natural killer cells [19].

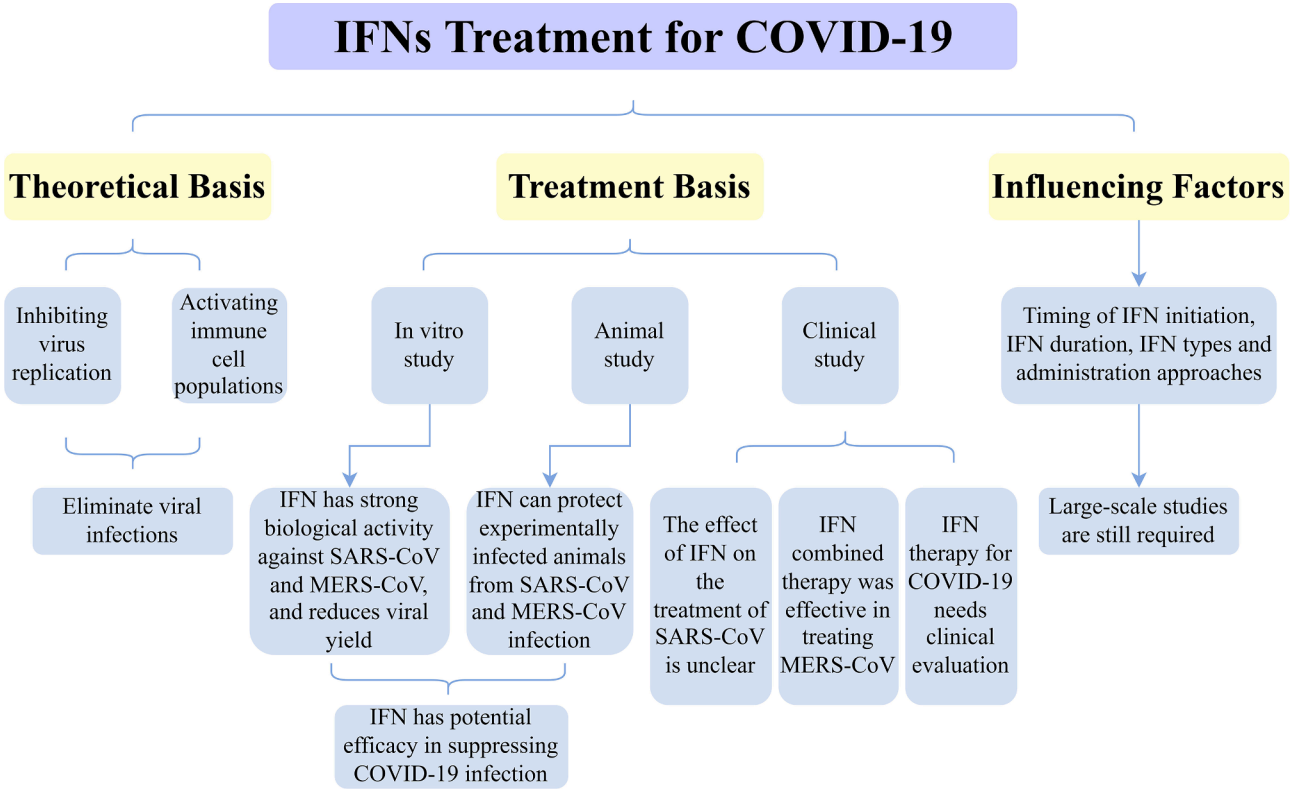

Fig. 1. Current research prospects of interferon treatment for COVID-19.

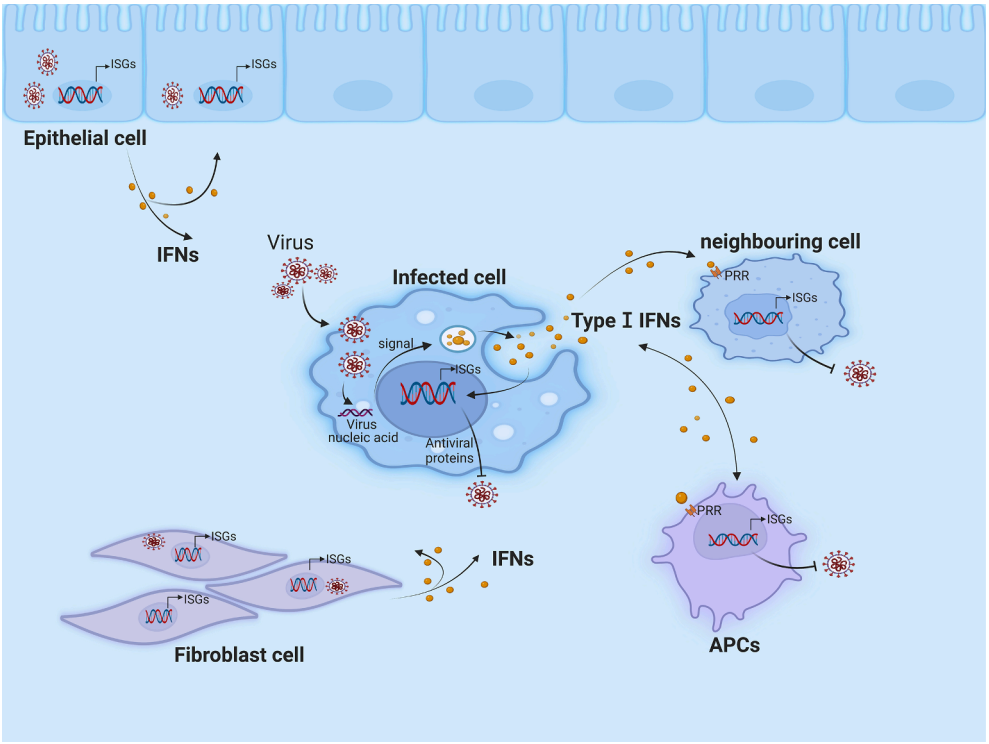

Fig. 2. Antiviral mechanism of interferon. Abbreviations: IFNs, interferons; ISGs, IFN-stimulated genes; PRR, pattern recognition receptor; APCs, antigen-presenting cells.

IFNs are ideal candidates as broad-spectrum antivirals because they exert direct and extensive effects on viral replication together with critical effects on the development and activation of immune cell subsets [19].

CoVs, however, encode an unusually large number of proteins and other factors that facilitate their survival and replication in the host despite the presence of effective host defense mechanisms, making the virus highly pathogenic [30]. In the past decades, tremendous progress has been achieved toward the understanding of anti-IFN activities against CoVs in humans [30,31]. Like most metazoan viruses, CoVs can attenuate the antiviral IFN signals through a multitude of passive and active mechanisms [32]. The nucleocapsid protein of SARS-CoV inhibits IFN-β production and counteracts host defense systems [33]. MERS-CoV can inhibit the body's ability to recognize the virus, antagonize induction of IFN responses, and block ISGs production until peak viral titers are achieved [6,34,35]. Consequently, antigen presentation of the virus and adaptive Th-1 immune responses against the virus diminish with a depressed IFN response [36]. Thus, CoVs undergo immune evasion in the host probably by reducing the IFN response.

Fortunately, the antagonistic activity of the virus against the IFN response, which is imperfect, usually delays the response induction rather than completely suppressing it [32]. Additionally, SARS-CoV and MERS-CoV are sensitive to exogenously administered IFNs [21,37]. In a genome-wide association study, analysis of the viral phenotype in 81 patients with COVID-19 revealed associations with IFN pathways, including SARS-CoV and innate immunity [38]. Notably, MERS-CoV is substantially more sensitive to IFNs than SARS-CoV as demonstrated in a cell culture study [39]. Based on the aforementioned rational and reliable evidence, recombinant IFNs are potentially suitable candidates for COVID-19 treatment.

4. Nonhuman studies

IFNs have been used for COVID-19 treatment based on evidence from (i) in vitro experiments; (ii) animal models; and (iii) limited clinical data for SARS, MERS, or COVID-19. As mentioned above, IFN response plays a key role in host defense mechanisms against viral invasion. Evidence from in vitro and animal models has confirmed that IFNs improve treatment outcomes in CoV infection.

4.1. *In vitro study*

The cytopathic effects (CPEs) of SARS-CoV can be inhibited by IFN-α, IFN-β, IFN-γ, or IFN-λ in vitro [40–45]. Of these, IFN-β has the highest potency when compared with IFN-γ and IFN-α [36]. Cinatl et al. assessed the inhibitory potential of recombinant IFNs against two clinical isolates of SARS-CoV in Vero and Caco2 cells and reported that IFN-β had a higher anti–SARS-CoV activity than the other IFN types [40], consistent with the findings of several studies [42,46–48]. This finding confirms the prophylactic protective and antiviral effects of IFN-β in SARS-CoV infection. Furthermore, substances that stimulate IFN production in human peripheral blood mononuclear cells, such as CpG oligodeoxynucleotide (BW001), could produce highly protective effects against SARS-CoV infection [49]. Some studies have indicated that IFN-α/-β combined with ribavirin [44,50] and IFN-β combined with IFN-γ can synergistically exert inhibitory effects on the replication potential of SARS-CoV [43,51]. For instance, IFN-β combined with IFN-γ inhibited SARS-CoV plaque formation by 30-fold and SARS-CoV replication by 3000-fold compared with the data obtained when these drugs were used as monotherapy [43,51]. Additionally, IFN-γ (100 IU/ml) combined with IFN-β1b (at a relatively low concentration [137 IU/ml]) adequately restricted viral replication by 93%, whereas monotherapy of these drugs could only marginally abate viral replication [51].

IFNs (-α, -β, -γ, and -λ) are considered effective against MERS-CoV in vitro [36]. Among them, IFN-β has the strongest biological activity against MERS, reducing viral titers very effectively with an IC_{90} value of 39 IU/ml [52]. IFN-α, similar to pegylated (PEG)-IFN-α, at a dose of 30 ng/ml could completely inhibit CPEs and reduce viral RNA levels in Vero cells [53]. Recently, the protective effect of IFN-λ gained recognition. Jeon et al. quantified the mRNA levels after MERS-CoV infection

and reported that IFN-λ is predominantly produced in the respiratory epithelium, and IFN-λ4, which has the highest potency to induce a response among all IFN types, demonstrated a remarkable suppressive effect on MERS-CoV replication and ISG expression [54]. Moreover, the type of drug combination was also considered for improved management of patients with MERS. Falzarano et al. reported that IFN-α2b combined with ribavirin, when administered at a lower concentration, could decrease the replication potential of MERS-CoV compared with monotherapy of the drugs when administered at a higher concentration individually; this finding indicates that the combination regimen facilitated a reduction in the drug concentration by 8-fold and 16-fold, respectively, to obtain a comparable endpoint with monotherapy [55]. Intriguingly, immunosuppressants combined with IFNs were highly effective against the virus. Cyclosporine combined with IFN-α1 reduced the viral titer more saliently than monotherapy of the drugs [56]. Additionally, mycophenolic acid, when combined with IFN-β1b, decreased the EC_{50} of IFN-β1b [57]. Nevertheless, contradictory results have also been reported. Sheahan et al. reported that lopinavir/ritonavir (LPV/RTV) did not boost the antiviral ability of IFN-β and had no effect on viral replication or severe lung pathology, although the combination regimen (LPV + RTV + IFN-β) could improve pulmonary function [48].

Treatment with IFN-α or IFN-β at a dose of 50 IU/ml reduced SARS-CoV-2 titers by 3.4 log or more than 4 log, respectively, in Vero cells [58]. When compared with SARS-CoV, SARS-CoV-2 has greater sensitivity to IFN-α [59]. Furthermore, among 22 antiviral agents, type I and II recombinant IFNs have the highest potency against SARS-CoV-2 in terms of viral antigen expression, viral load reduction, and plaque reduction ability in VeroE6 cells [60]. These results collectively suggest the potential efficacy of human IFN in suppressing SARS-CoV-2 titers.

4.2. Animal study

Direct IFN treatment or in combination demonstrated protective effects against SARS-CoV or MERS-CoV in experimentally infected mice, marmosets or macaques when administered subcutaneously or intranasally [26,55,61–65]. Haagmans et al. confirmed the in vivo anti–SARS-CoV activity of PEG-IFN-α in macaques, wherein PEG-IFN-α effectively hindered viral replication, viral antigen expression by type I pneumocytes, and pulmonary damage [61]. IFN combined with ribavirin and/or lopinavir was effective against MERS-CoV in rhesus macaques [55] and common marmosets [62]. Falzarano et al. demonstrated that IFN-α2b and ribavirin partly prevented disease progression to pneumonia and reduced viral genome copy number and gene expression levels in rhesus macaques after infection with MERS-CoV [55]. IFN-β1b and lopinavir, either alone or in combination, could protect marmosets from the adverse effects of MERS-CoV infection in terms of clinical, radiological, and pathological parameters, and the combination showed a better inhibition of viral replication, mitigation of host responses, and improvement of treatment outcomes [62].

However, Sheahan et al. recently reported that IFN-β combined with LPV/RTV exhibited weak antiviral activity against MERS-CoV in vitro and in vivo when compared with that of remdesivir [48]. The authors also reported that subcutaneous administration of IFN-β every other day failed to decrease the MERS-CoV load and exacerbated the infection in mice [48]. Animal model type, route of administration, and IFN subtype may contribute to inconsistent results among the studies. Therefore, during IFN treatment, the SARS-CoV-2 replication cycle should be evaluated in animal models and/or clinical trials.

5. Clinical data of treatment with IFNs for COVID-19

5.1. IFN treatment of SARS

Patients with SARS are treated with IFNs combined with corticosteroids and antibiotics [8]. In a preliminary open-label, uncontrolled study, in which corticosteroids were used to treat SARS, patients who also received IFN alfacon-1 had improvement in radiographic lung abnormalities and recovered oxygen saturation levels more quickly than those who received corticosteroids alone [9]. Moreover, the authors reported that patients who took concomitant medications had a lesser increase in creatine kinase levels and a more rapid restoration of lactate dehydrogenase levels to the normal range [9]. However, Zhao et al., in their study, treated patients with SARS with recombinant IFN-α combined with corticosteroids or antibiotics but did not observe the therapeutic benefit of IFN-α [66]. As no new cases have been reported, no further evidence can clarify the therapeutic effects of IFNs on SARS more clearly.

5.2. IFN treatment for MERS

IFNs have been more often used for MERS treatment than for SARS treatment. Routine injections of IFN-β1b have been recommended as the first choice of treatment [67]. According to the treatment guidelines for MERS stipulated by Korea, PEG-IFN-α2a can be used at a dosage of 180 μg/week for 2 weeks unless renal replacement therapy is involved [68].

The combination of IFNs and other antiviral drugs to treat MERS has been described in several case reports [69–71] and retrospective cohort studies [69,72–75]. In a case study, PEG-IFN-α2a, LPV/RTV, and ribavirin were combined to treat MERS-CoV infection in South Korea, and the results showed satisfactory viral clearance and host survival [70]. Moreover, the survival of patients with severe MERS-CoV infection was improved when treated with IFN-α2a and ribavirin [74]. The effects of IFNs combined with ribavirin are well documented [57,69,72,76].

Conversely, some studies demonstrated poor or adverse outcomes in patients with MERS who received IFN treatment. For critically ill patients with MERS, different IFN subtypes (rIFN-α2a, rIFN-α2b, or rIFN-β1a) and ribavirin were commonly used, but the drugs did not have any effect on the reduction in 90-day mortality or faster MERS-CoV RNA clearance [77]. Omrani et al. reported that patients with severe MERS-CoV infection who were on mechanical ventilation and who received PEG-IFN-α2a and ribavirin early in the treatment had a higher 14-day survival rate (P =.004), but the difference in the 28-day survival rates between the combination medication and standard care was not statistically significant (P =.054) [74]. Another retrospective observational study conducted in Saudi Arabia (n = 51) revealed that therapy with IFN-β and mycophenolate mofetil for MERS was associated with a lower mortality rate in univariate analysis but not in multivariate analysis [78]. Although past systematic reviews did not report consensus findings on the efficacy of IFN treatment for MERS [79,80], currently, a randomized controlled trial (RCT) that evaluated 95 people demonstrated that IFN-β combined with LPV/RTV led to a lower 90-day mortality rate than placebo when used within 7 days after symptoms manifestation, which provides strong evidence to support the clinical efficacy of IFN [81].

5.3. IFN treatment for COVID-19

Given the history of IFNs in the treatment of SARS and MERS, IFN-α is used early, especially at treatment initiation, in COVID-19 treatment [82]. In the least official version of the diagnosis and treatment protocol for COVID-19 issued by China, IFN-α is still recommended for antiviral therapy through nebulization (5 million units per time for adults in sterile injection water, twice a day) [83]. This special administration route may have been chosen avoid the adverse effects of subcutaneous IFN therapies [14], such as adverse reactions due to IFN injections (fever, chills, myalgia and headache), neuropsychiatric problems, and hypersensitivity reactions as observed in a randomized clinical trial [84]. Although accumulating evidence suggests that subcutaneous injection of IFN can increase host survival rate, alleviate symptoms, and decrease hospital length of stay when combined with other medications [84–88], some researchers have thought highly of nebulized IFNs for its higher pulmonary concentration and lower systemic side effects.

Inhalation treatment with IFN-β-1b and LPV/RTV successfully cured patients who had a worsening respiratory status after antibiotic and hydroxychloroquine treatment failed to reverse COVID-19 progression [89]. In a retrospective cohort study of 466 patients, treatment with aerosolized IFN-α2b within 5 days since hospital admission lowered in-hospital mortality risk [90]. Another double-blind RCT showed that nebulized IFN-β1b had greater prospects of conferring rapid improvement and recovery [91]. In a systematic review and *meta*-analysis, several RCTs consistently reported that IFN-β treatment can lower intensive care unit admission risk by 42% and increase the discharge rate by 3.05-fold in patients with COVID-19, thus supporting its use as a safe therapy for COVID-19 [92,93].

However, some trials recommend the avoidance of treatment with IFNs because the IFNs did not demonstrate any synergistic effect when combined with other drugs or therapies [94–96]. Meanwhile, patients with COVID-19 receiving IFN-β-1b treatment may experience elevated anti thyroid peroxidase levels and thyroid dysfunction [97]. Owing to heterogeneous results, treatment with IFNs for COVID-19 warrants further clinical evaluation.

6. IFN efficacy and possible influencing factors

As mentioned earlier, in vitro experiments, animal models, and clinical studies have provided inconsistent evidence on the efficacy of IFNs against MERS, as observed in a systematic review and *meta*-analysis; the mortality rate of patients who received IFNs (α2a, α2b or β1a) combined with ribavirin was equivalent to that of those who received supportive treatment only [79]. This discrepancy between in vitro and in vivo findings may be attributed to the high EC50/Cmax ratio of the drugs and the late timing of IFN therapy [36,98]. Clinical studies on patients with SARS or MERS report heterogeneous findings, varying in terms of timing of IFN administration, type of patient population assessed, stage of disease, type of IFN used (PEGylated or short-acting), and so on [3,12,36,98]. Similarly, the largest clinical trial of COVID-19 to date, namely, the Solidarity Trial, reported highly controversial results. The trial indicated that IFN-β-1a, remdesivir, hydroxychloroquine, and LPV/RTV regimens were barely conducive to overall mortality or the in-hospital clinical course [95], but as the trial prioritized broad access, people were recruited regardless of significant heterogeneity in therapy implementation, controls (standard care depended on which drugs were used and at what time they were locally available), patient populations, and their clinical conditions. Consequently, whether the results are conclusive remains uncertain [99]. An open-label RCT in which the subjects had more similar background characteristics also supported the finding that IFN-β-1a failed to improve either the clinical status or viral clearance, but the study also confirmed the absence of patients who were in the early phase of COVID-19 [96]. The viral kinetics of respiratory specimens cannot be determined, as most studies conducted on humans are case studies, the tolerability of the IFN regimen by patients with MERS has not been sufficiently evaluated, and the viral load has not been quantified [70]. Furthermore, patients were simultaneously treated with other antivirals, antibiotics, steroids, and invasive or noninvasive ventilation, and IFNs were even administered prophylactically in some cases [69]. We cannot exclude the possibility of spontaneous improvement in these studies, although many patients recovered after receiving IFN antiviral therapy. Thus, the efficacy of IFN treatment from these clinical reports remains controversial, and recommendations for therapy have been barely made.

Several factors described above may affect the clinical outcome of IFN therapy. First, the timing of IFN response induction determines the clinical course of the disease [100]. IFN treatment initiation after 10 days since symptom onset barely exerted any therapeutic effect (Table 1) [68,75], which is probably attributed to the viral load. In the initial stage of infection, the viral load is adequately low for the IFNs to counteract, whereas, in disease exacerbation, the IFN response is thwarted and delayed by the virus, almost always leading to hyperinflammation and tissue damage [101]. When IFN-β-1b treatment was limited within 7 days, the addition of IFN-β-1b demonstrated safety and superior effects to those of LPV/RTV alone in terms of alleviating symptoms and shortening hospital length of stay in patients with mild-to-moderate COVID-19 [87]. Second, the association between various durations of IFN treatment and clinical outcomes has not yet been validated in double-blind RCTs. Currently, the optimal duration is decided according to the patient's conditions; hence, further well-designed studies evaluating the effects of IFN duration on treatment outcomes in COVID-19 are urgently needed. Third, IFNs are usually been combined with ribavirin or LPV/RTV; thus, the elucidation of data was hindered mainly by various combinations of regimens. Given the lack of convincing clinical evidence, no particular IFN is superior to the other types [72], although a three-arm, open-label RCT reported that IFN-β1a, rather than IFN-β1b, significantly shortened the time to clinical improvement [102], and such conclusion should be interpreted with more caution. Another study that suggested the use of IFN-λ for patients with COVID-19 also raised concerns regarding the control of the "cytokine storm" emerging during IFN treatment [103]. In addition, critically ill patients with multiple immunosuppression-associated comorbidities, such as chronic kidney disease, may not benefit from IFN antiviral therapy [72,75,100]. It is therefore necessary to screen all patients and identify who would most benefit from IFN treatment. Further large-scale studies are required, considering the effect of all possible factors including the timing of IFN initiation, IFN treatment duration, IFN type used, and the clinical condition of patients with COVID-19.

7. Conclusion

In this review, we summarized published literature on IFN treatment for COVID-19. As broad-spectrum antiviral agents, IFNs not only directly inhibit viral replication but also activate immune cell subsets, thus providing a potential theoretical benefit for COVID-19 treatment. They are clinically well-established agents and routinely available. Currently available IFN therapies for COVID-19 are mainly adapted from those used for SARS-CoV or MERS-CoV, but in vitro and animal studies have mostly assessed their effects. Regardless of the satisfactory outcomes of these in vitro and nonhuman primate studies, the limited number of case studies or retrospective studies does not provide overall firm evidence concerning the efficacy or safety of IFN therapy per se for CoVs, owing to the lack of well-designed and controlled clinical trials. Moreover, the timing of IFN treatment initiation, the duration of treatment, the IFN type used, and other pivotal factors of IFNs may affect the outcomes of CoV treatment, thereby being worthy of further investigation. In the scenario of the ongoing dangerous CoV outbreak, providing convincing positive or negative findings will be critical for treatment. Thus, the findings of this review may serve as the basis for future clinical trials of IFN treatment for COVID-19.

CRediT authorship contribution statement

Dan Ma: Data curation, Formal analysis, Writing – original draft. **Ximin Wang:** Data curation, Visualization. **Min Li:** Visualization, Investigation, Writing – review & editing. **Chujiao Hu:** Conceptualization, Methodology. **Lei Tang:** Conceptualization, Methodology.

Author contributions

The corresponding authors, LT drew up the outline. DM, ML and XMW searched information to draft the manuscript and redacted it. All authors contributed to the idea for the review and agreed to the submitted version. CJH and LT are the guarantors.

Table 1
Clinical studies of IFN against COVID-19.

Virus infection	Study Design	IFN Treatment Regimen	Combined antiviral drug	Time of IFN initiation	Time of IFN duration	Results	References
SARS-CoV	Retrospective cohort study (n = 22)	IFN alfacon-1 (9 μg/day for the first 2 days and increased to 15 μg/day if no response)	none	A median of 8 days (IQR 4–10) after symptom onset	10 days	Reduced disease-associated impaired oxygen saturation, more rapid resolution of radiographic lung abnormalities and lower levels of creatine kinase	(Loutfy et al., 2003)
SARS-CoV	Cohort study (n = 190)	IFN-α (3 million IU/day)	none	Unknown	Unknown	Less effective than the early use of steroids	(Zhao et al., 2003)
MERS-CoV	Case series (n = 2)	PEG-IFN alfa-2a (180 μg/week)	RBV	The admission day	2 weeks	Recovery	(Khalid et al., 2014)
MERS-CoV	Case report (n = 1)	PEG-IFN-α2a (180 μg/week)	LPV/r and RBV	15 days after cough; 4 days after admission; >4 days after fever	1 week	Recovery	(Kim et al., 2016)
MERS-CoV	Case report (n = 1)	PEG-IFN (180 μg//week)	LPV/r and RBV	13 days after symptom onset	12 days	Died	(Spanakis et al., 2014)
MERS-CoV	Case report (n = 1)	PEG-IFN-α2a (180 μg/week)	RBV	12 days after symptom onset	1 week	Died	(Malik et al., 2016)
MERS-CoV	Retrospective observational study (n = 2)	PEG-IFN-α2a (180 μg//week) or PEG-IFN-α2b (1.5 μg/kg/week)	RBV	11 days after symptom onset	2 or 3 weeks	The 1st patient improved and were discharged while the 2nd patient died	(Ha et al., 2015)
MERS-CoV	Case series (n = 6)	IFN-α2b (180 μg /week)	RBV	1–2 days from onset in survivals and 12–19 days in those who died	2 weeks	3 patients who had comorbid conditions died, and 3 survived	(Khalid et al., 2014)
MERS-CoV	Retrospective observational study (n = 5)	IFN-a2b (100 μg, 130 μg or 144 μg/week)	RBV	A median of 19 days (range 10–22)	100 μg for 2 weeks; 130 μg or 144 μg once	All died	(Al-Tawfiq et al., 2014)
MERS-CoV	Retrospectivecohort study (n = 44)	PEG-IFN alfa-2a (180 μg/week)	RBV	A median of 3 days (range 0–8) from diagnosis of MERS-CoV infection.	2 weeks	**Improved survival at 14 days but not at 28 days**	(Omrani et al., 2014)
MERS-CoV	Retrospectivecohort study (n = 32)	IFN-a2a (180 μg/week) Or IFN-b1a (44 μg, 3 times/ week)	RBV	Within 1 day following MERS-CoV diagnosis	IFN-a2a for a median duration of 6 days and IFN-b1a for a median duration of 6.5 days	The overall mortality rate was **85%** (11/13) in the IFN-a2a group and **64%** (7/11) in the IFN-b1a group (P = 0.24); the lack of efficacy of IFN-a2a or IFN-b1a with RBV in treating MERS-CoV	(Shalhoub et al., 2015)
MERS-CoV	Retrospective cohort study (n = 349)	PEG-rIFN-α2b (1.5 μg/kg/week for 2 weeks); PEG-rIFN-α2a (180 μg/week for 2 weeks);rIFN-β1a (44 mg, 3 times/ week)	RBV	A median of 2 days from ICU admission, which corresponded to 5 days from hospital admission and 9.0 days from onset of symptoms	A median of 8 days	IFN combined with RBV was not associated with reduction in 90-day mortality or in faster MERS-CoV RNA clearance	(Arabi et al., 2019)
MERS-CoV	Case series (n = 14)	IFN-α2a (180 μg/ week)	RBV	6 days from symptom onset	A maximum of 2 weeks	Survival of all patients but no conclusion on IFN efficacy	(Khalid et al., 2016)
MERS-CoV	Observational study (n = 51)	IFN-α or IFN-β (Dosage was unclear)	RBV or mycophenolate mofetil	Unknown	Unknown	IFN-β and mofetil improved survival; **The use of IFN-β and IFN-α was associated with survival rates of 78.3%, 75%**	(Al et al., 2016)
MERS-CoV	Retrospective cohort (n = 314)	IFN (subtype and dosage were unclear)	RBV	Unknown	Unknown	The use of interferon-RBV was not associated with mortality.	(Alfaraj et al., 2019)
MERS-CoV	Prospective cohort study (n = 8)	IFN-α2b (Dosage was unclear)	RBV and oseltamivir	Unknown	Unknown	5 patients expired, 2 were discharged alive, and 1 remained intubated at the end of the study period	(Al-Hameed et al., 2016)
SARS-CoV-2	Open-label, RCT (n = 81)	IFN-β1a (44 μg/m/ dose, 3 times weekly)	HCQ plus LPV/r or atazanavir/ ritonavir	A median time of 10 days after symptoms onset (IQR 8–13)	2 weeks	In IFN group, discharge rate on day 14 significantly was rose and 28-day mortality also was reduced	(Davoudi-Monfared et al., 2020)
SARS-CoV-2	non-controlled prospective trial (n-20)	IFN-β1a (44 μg/dose, q.o.d)	HCQ and LPV/r	The admission day (the time before symptom onset < 7 days)	10 days	Virological clearance significantly was decreased and imaging	(Dastan et al., 2020)

(*continued on next page*)

Table 1 (*continued*)

Virus infection	Study Design	IFN Treatment Regimen	Combined antiviral drug	Time of IFN initiation	Time of IFN duration	Results	References
						records was improved significantly in all patients	
SARS-CoV-2	Observational study (n = 41)	IFN-α2b (3 million IU/time, q.o.d)	LPV/r	For early intervention, IFN was applied within 72 h of admission, while for late intervention, IFN was took after 72 h of admission)	10 days	Virus clearance was accelerated and the average time of hospitalization was decreased. Early IFN intervention was better than delayed treatment as indicated by the days of hospitalization	(Wang et al., 2020)
SARS-CoV-2	Open-label, phase 2, RCT (n = 127)	IFN-β1b (3 doses of 8 million IU, q.o.d)	LPV/r and RBV	A median of 5 days after symptoms onset (IQR 3–7)	2 weeks	No patients died and IFN group was associated with a significant reduction in the duration of viral shedding, symptom alleviation and shorter duration of hospital stay than control group	(Hung et al., 2020)
SARS-CoV-2	Open-label, RCT (n = 66)	IFN-β1b(250 μg, q.o.d)	HCQ plus LPV/r or atazanavir/ritonavir	The admission day (a median time of 7 days from symptom onset to admission, IQR 5–9)	2 weeks	With IFN-β-1b treatment, ICU admission rate, the need for invasive mechanical ventilation and 28-day mortality was significant lower	(Rahmani et al., 2020)
SARS-CoV-2	Case series (n = 4)	IFN-β1b (9.6 million IU/dose/day)	LPV/r or HCQ	The admission day	10–13 days	All were discharged and alive	(Mary et al., 2020)
SARS-CoV-2	Retrospective multicenter cohort study (n = 446)	IFN-α2b (Dosage was unclear)	LPV/r, or umifenovir	For early IFN, the median time from admission to first dose was 2 days (IQR 1–2), while for late IFN, the median time was 8.5 days (IQR 7–11)	A median of 10 days	As for mortality rate, early administration of IFN exerted better effect than late IFN therapy. And IFN was associated with faster recovery than LPV/r	(Wang et al., 2020)
SARS-CoV-2	Double-blind, phase 2, RCT (n = 98)	IFN-β1a (6 million IU/dose/day)	Unknown	The admission day (a median duration of 10 days of COVID-19 symptoms, IQR 7–11)	2 weeks	None patients died in IFN group and IFN increased the odds of recovery	(Monk et al., 2021)
SARS-CoV-2	Double-blind, phase 3, RCT(n = 969)	IFN-β1a (44 μg/dose, q.o.d)	Unknown	The admission day (a mean duration of 8.7 days from symptoms onset before enrolment)	Up to 4 doses	The addition of IFN-β1a didn't show more benefit than using remdesivir alone	(Kalil et al., 2021)
SARS-CoV-2	Open-label RCT (n = 11,330)	IFN-β1a (44 μg/dose, subcutaneous on the day of randomization and days 3 and 6 or 10 μg intravenously daily)	With or without lopinavir	The randomization day	6 days	IFN-β1a didn't benefit COVID-19 patients in terms of overall mortality, initiation of ventilation, and length of hospital stay	(WHO, Solidarity Trial Consortium et al., 2021)
SARS-CoV-2	Open-label RCT (n = 583)	IFN-β1a (44 μg/dose)	LPV/r	The randomization day (a median time of 9 days from symptom onset to randomization, IQR 7–12)	On day 1, 3 and 6	No significant effect	(Ader et al., 2021)
SARS-CoV-2	Open-label RCT (n = 60)	IFN-β1a (12,000 IU) or IFN-β1b (8 million IU	HCQ plus LPV/r	The randomization day (a median time of 5 days from symptom onset to randomization, IQR 3–7)	On day 1, 3 and 6	Patients with IFN-β1a rather than IFN-β1b showed clinical improvement more quickly than patients in control	(Alavi Darazam et al., 2021)

Abbreviations: LPV/r, lopinavir/ritonavir; RBV, ribavirin; rIFN, recombinant IFN; HCQ, Hydroxychloroquine; IQR, interquartile range.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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